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DRUG DISCRIMINATION UNDER A CONCURRENT FIXED-RATIO FIXED-RATIO SCHEDULE

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Pigeons were trained to discriminate 5.0 mg/kg pentobarbital from saline under a two-key concurrent fixed-ratio 10 fixed-ratio 40 schedule of food presentation, in which the fixed-ratio component with the lower response requirement was programmed to reinforce responding on one key after drug administration (pentobarbital-biased key) and on the other key after saline administration (saline-biased key). After responding stabilized, pigeons averaged 98% of their responses on the pentobarbital-biased key during training sessions preceded by pentobarbital, and they averaged 90% of their responses on the saline-biased key during training sessions preceded by saline. In test sessions preceded by doses of pentobarbital, chlordiazepoxide, or ethanol, pigeons switched from responding on the saline-biased key at low doses to responding on the pentobarbital-biased key at higher doses (the dose–response curve was quantal). High doses of phencyclidine produced responding on both keys, whereas pigeons responded almost exclusively on the saline-biased key after all doses of methamphetamine. These and previous experiments using concurrent reinforcement schedules to study drug discrimination illustrate that the schedule of reinforcement is an important determinant of the shape of dose–effect curves in drug-discrimination experiments.

Key words: drug discrimination, concurrent fixed-ratio schedules, matching law, CNS depressants, CNS stimulants, key peck, pigeons

There has been considerable disagreement among drug-discrimination researchers as to whether drug discrimination is a continuous variable or a discrete one (Colpaert, 1985, 1991; Holloway & Gauvin, 1989; Mathis & Emmett-Oglesby, 1990; Stolerman, 1991). For example, Colpaert (1991) argued that the relationship between a drug stimulus and a response is an ''all-or-nothing'' relationship (usually referred to as a quantal response, which is measured on a nominal scale). In contrast, Holloway and Gauvin and Stolerman have suggested that whether the drug discrimination is graded or quantal depends on the conditions under which the experiment is conducted. One of the most important of these conditions is the schedule of reinforcement.

Most drug-discrimination research has employed fixed-ratio (FR) schedules to maintain responding. Responses on one operandum are reinforced after drug administration and on another after saline administration (Colpaert, 1986; Overton, 1984). Holloway and Gauvin (1989) and Stolerman (1991) have presented evidence that the schedule of reinforcement can be a determinant of the shape of dose–response curves in drug-discrimination generalization experiments. Holloway and Gauvin suggested that schedules that maximize reinforcer delivery when responses are confined to one alternative (e.g., simple FR schedules) generate quantal responding on one operandum, whereas schedules that maximize reinforcer delivery when animals distribute their responses across alternatives generate a graded distribution of responses across these alternatives. During drug-discrimination training, responses on the drug-paired operandum are reinforced exclusively in the presence of the training drug and responses on the other operandum are reinforced only in its absence. It is possible that this all-or-nothing relationship between the presence or absence of the drug and the delivery of the reinforcer during training sessions may influence the shape of the drug-discrimination generalization curve regardless of the schedule under which the reinforcer is delivered (Colpaert, 1985, 1987; Mathis & Emmett-Oglesby, 1990).

To determine the role of the schedule of reinforcement in drug-discrimination exper-

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iments, we have compared responding maintained by fixed-interval (FI) schedules, with responding maintained by FR schedules (Massey, McMillan, & Wessinger, 1992; McMillan & Hardwick, 1996; Snodgrass & McMillan, 1991). In one study, rats were trained to discriminate 10 mg/kg pentobarbital from saline under a multiple FR 20 FI 180-s schedule of food reinforcement. Under the FR component of the multiple schedule, the pentobarbital dose–response curve was characterized by responding that was almost entirely on the saline-paired key at low doses and almost entirely on the drug-paired key after higher doses (Snodgrass & McMillan, 1991). In contrast, the pentobarbital dose–response curve under the FI component of the schedule was characterized by graded responding, with an increasing proportion of responses occurring on the drug key as the dose increased in individual animals. These results were replicated using a different training drug (5.0 mg/kg morphine), different FI and FR reinforcement schedules, and a different species (pigeons) (Massey et al., 1992). At the low FR values used by Snodgrass and McMillan, reinforcer delivery occurred at much shorter intervals than occurred under the FI component of the multiple schedule; however, the study by Massey et al. suggested that this difference in reinforcement frequency under FR and FI schedules was not a major determinant of the shape of the generalization curve. In this study, the frequency of reinforcer delivery was approximately equal under the FI and FR schedules, yet the difference in the pattern of responding maintained by the schedules persisted. More recently, McMillan and Hardwick (1996) systematically manipulated the size of the FR and FI components of a multiple schedule in pigeons trained to discriminate 5.0 mg/kg pentobarbital from saline. Under FI schedule components, the pentobarbital dose–response curve was continuous across a wide range of FI values. Under the FR components, responding was quantal with lower FR requirements, but appeared to become continuous as the size of the FR requirement increased to a point at which ratio strain was apparent.

Snodgrass and McMillan (1991) suggested that drug-discrimination experiments could be viewed as choice behavior. During training, subjects have a choice between two operanda. If responding on one operandum delivers the reinforcer under an FR schedule while responding on the other operandum is never reinforced, the schedule can be viewed as a concurrent FR extinction schedule with responses on one operandum reinforced under the FR component and responses on the other extinguished. The discriminative stimulus in the presence of which responses will be reinforced under the FR schedule component is determined by the presence or absence of the drug. Similarly, when drug-discrimination responding is maintained under an FI schedule, the schedule can be viewed as a concurrent FI extinction schedule.

When stimulus control is strong, responding under concurrent FR extinction and concurrent FI extinction schedules would not necessarily lead to very different predictions. For example, under both FR and FI schedules of reinforcement, low doses of the training drug might not produce discriminable stimuli, and this would lead to responding largely confined to the saline key, whereas high doses of the training drug would be easily discriminable and would lead to responding on the drug key. At intermediate doses of the training drug, however, the presence or absence of the training stimulus may be ambiguous, such that the schedule of reinforcement becomes the dominant independent variable determining the subject's choice behavior. Recent studies by Davison and Jones (1998) have suggested that responding under concurrent variable-interval (VI) extinction schedules is not exclusive to the VI alternative, especially if the discriminability of the stimuli is less than perfect.

In choice experiments involving two operanda, the relative distribution of responses across the two alternatives often has been described by the matching law (Herrnstein, 1970). According to the generalized matching law (Baum, 1979), responding under concurrent interval schedules approximately matches the relative rate of reinforcement of these responses (Davison & McCarthy, 1988). Under concurrent ratio schedules, reinforcer frequency is maximized by confining responding exclusively to the operandum programmed to deliver the reinforcer under the smaller of the two ratio values. Applying these concepts to drug-discrimination procedures

that use FR schedules, after saline the drug stimulus is not present, so responding is confined to the saline operandum. After the training dose of a drug (and perhaps higher doses) the drug stimulus is present and responding is confined to the drug operandum. In both of these cases, the schedule can be considered to be a concurrent FR extinction schedule. However, at some doses lower than the training dose, the drug stimulus is weaker than that produced by the training dose. Under these conditions, responding might be considered to be under the control of a concurrent FR FR schedule, because the drug stimulus may not provide the cue for differential reinforcement on the two response keys. Under concurrent FR FR schedules, animals might be expected to confine their responses to one of the two operanda (Davison & McCarthy, 1988; Herrnstein & Loveland, 1975). In contrast, under concurrent interval schedules animals might be expected to respond on both keys after administration of doses that produce weak stimulus control. This might explain why drug-discrimination responding maintained under an FR schedule generates all-or-nothing dose–response curves and drug discrimination under FI schedules generates graded dose–response curves in drug substitution tests.

The preceding analysis is based on the unproved assumptions that in the middle of the dose–response curve there is a loss of stimulus control by the drug, which causes the response pattern to come under greater control by the reinforcement schedule. To determine whether these explanations are plausible it would be necessary to study drug discrimination under concurrent reinforcement schedules. Snodgrass and McMillan (1996) trained pigeons to discriminate the presence or absence of 5.0 mg/kg pentobarbital using a concurrent VI VI schedule. Under this schedule, relative reinforcement contingencies were in effect. When the training drug was administered, responses on the pentobarbital-biased key were reinforced more frequently than responses on the other key (saline-biased key). When saline was administered, responses on the saline-biased key were reinforced more frequently than responses on the pentobarbital-biased key. Under these conditions, increasing doses of pentobarbital produced graded increases in the percentage of responses on the pentobarbital-biased key. More recently, these findings have been replicated using concurrent FI FI schedules in pigeons (McMillan, Li, & Hardwick, 1997). The purpose of the present series of experiments was to study drug discrimination under concurrent FR FR schedules. Responding under concurrent FR FR schedules should result in responding confined largely to one of the two response keys. According to the hypothesis of Snodgrass and McMillan (1996), under concurrent FR FR schedules, the dose–response curve for the training drug should be all or nothing, with responding after low doses occurring primarily on the saline-biased key with a shift to responding on the drug-biased key at higher doses. Finally, the use of concurrent FR FR schedules should provide evidence as to whether all-or-nothing responding develops in drug-discrimination experiments because responses on the drug key after vehicle administration never produce the reinforcer (Colpaert, 1985), or because interval and ratio schedules of reinforcement produce different shapes of dose–response curves.

Pentobarbital was selected as the training drug for these experiments so that the results could be compared directly to our previous experiments in which pentobarbital was established as the discriminative stimulus under concurrent schedules (McMillan et al., 1997; Snodgrass & McMillan, 1996). Chlordiazepoxide and ethanol were substituted for pentobarbital in generalization tests because these drugs have been reported to substitute as a discriminative stimulus for pentobarbital in drug-discrimination studies (Colpaert, Desmedt, & Janssen, 1976). Methamphetamine was chosen because it has not substituted for pentobarbital as a discriminative stimulus, and phencyclidine (PCP) was chosen because it has substituted partially for pentobarbital in drug-discrimination tests (McMillan & Hardwick, 1996).

METHOD

Subjects

Four adult male White Carneaux pigeons (Palmetto Pigeon Plant), P339, P340, P341, and P342, served as experimental subjects. The pigeons were individually housed with free access to food and water in a tempera-

ture- and humidity-controlled room that was maintained under a 12-hr normal phase lighting cycle. After 100% body weights were determined over a 2-week period, the pigeons were reduced to, and maintained at, approximately 80% of these weights for the duration of the study. Supplemental food was provided after experimental sessions as necessary to maintain the 80% body weights (range, 452 to 467 g). Bird 342 died the day after the administration of the highest dose of methamphetamine, so data for this bird are available only for the first pentobarbital dose–response curve and for methamphetamine.

Apparatus

The experimental chamber was a Gerbrands Model G5610-A pigeon test cage enclosed in a Gerbrands Model G7211 sound- and light-attenuating cubicle. Two 28-V DC lights illuminated the experimental chamber during the session except during a food cycle when a light over the food hopper was illuminated. On the front panel of the cage, three Gerbrands response keys (Model G7311) were mounted 7 cm apart, 20 cm above the grid floor. The center key was not used in these experiments and remained darkened at all times. When operative, the left key was blue and the right key was yellow. A food hopper (Gerbrands), through which access to mixed grain could be given, was centered between the response keys at floor level. A microcomputer (Gateway 2000 Inc.), located in a room adjacent to the room containing the experimental chamber, controlled the reinforcement schedule and recorded the data through a MED Associates® interface.

Procedure

The pigeons were experimentally naive at the beginning of the study. After they had been reduced to 80% of their free-feeding weights, they were trained to peck the two response keys by an autoshaping procedure for two sessions and then were placed under an FR 1 schedule with only the blue (left) key lighted. After the pigeon had earned 50 reinforcers within a 40-min session with the blue key lighted, only the yellow (right) key was lighted during the next session and the FR 1 reinforcement schedule was in effect for responses on the yellow key. After earning 50 reinforcers within 40 min or less with the yellow key lighted, pigeons were exposed to a reinforcement contingency in which the key on which responses were reinforced under an FR 10 schedule alternated after each reinforcer delivery. Under this schedule both the left and right keys were transilluminated. When the left key was active, completion of 10 responses (FR 10) on that key produced reinforcement. Subsequently, when the right key was active, an FR 10 requirement had to be met on that key. This requirement of completing 10 responses on one key and then 10 responses on the other key continued until the pigeon earned 25 reinforcers on each key in one session. The purpose of this procedure was to limit the development of position preferences.

Discrimination training was initiated in the next phase. Pigeons were trained to discriminate pentobarbital (5.0 mg/kg im) from saline under a concurrent FR 10 FR 40 schedule of reinforcement. Following an intramuscular injection of 5.0 mg/kg pentobarbital or saline, birds were placed in the test chamber and a 10-min presession period followed. During this 10 min, the chamber lights were extinguished and key pecks were not recorded. At the end of the presession period, the houselights were illuminated and the schedule contingencies were initiated. During these discrimination training sessions, both the left and right keys were transilluminated, and a different FR schedule was operative on each key. Completion of either of the FR requirements resulted in delivery of the reinforcer (4-s access to mixed grain). After administration of the training drug, the FR 10 component was programmed on the right key (yellow key) and the FR 40 component was programmed on the left key (blue key) for Birds P339 and P340. After saline administration, the ratio with the lower response requirement was programmed on the left key (blue key) and the ratio with the higher response requirement was programmed on the right key (yellow key). For Birds P341 and P342, the reinforcement contingencies after administration of the training drug and saline were reversed. Training sessions continued until 50 reinforcers had been delivered or 40 min had elapsed. Responding was maintained under these concurrent FR 10 FR 40 schedules for the duration

of the study with the exception of control and test sessions, which will be described later.

To prevent reinforcement of switching between keys (Catania, 1966), a changeover delay (COD) of 3 s was imposed, such that a response could not produce a reinforcer unless it occurred at least 3 s after the bird switched to responding on the other key. Training sessions were conducted 6 days per week. During initial training, two drug training sessions were followed by two saline training sessions for 2 weeks, after which drug and saline training sessions alternated.

Test sessions were interspersed with training sessions when the subjects reached the training criterion: The pigeons had to complete at least 51% of their responses on the key paired with the FR 10 component for 20 consecutive training sessions (i.e., 10 each of pentobarbital and saline). This criterion had to be met for both pentobarbital and saline administration prior to the initiation of substitution testing with other drug doses. This criterion was reached by all birds after 55 sessions of training. Subsequently, test sessions during which other doses and drugs were administered, instead of the training dose of pentobarbital, were conducted on Tuesdays and Fridays, with training sessions continuing on other days. If a bird failed to reach criterion performance (at least 51% responding under the FR 10 component) on a training day, test sessions were postponed until the criterion had been met under both the pentobarbital and saline training conditions.

The procedure used during test sessions was similar to the procedure used during training sessions, except that during test sessions a concurrent FR 25 FR 25 schedule of reinforcement was in effect. This FR 25 value was chosen because it is intermediate between that of the FR 10 and the FR 40 schedule values used during training sessions. Because the pigeons had not been exposed to this reinforcement schedule during training sessions, the concurrent FR 25 FR 25 schedule was not likely to provide additional cues as to which response would be reinforced more frequently during test sessions. In addition to the other doses and other drugs that were administered during test sessions, the pentobarbital and saline training doses were administered under the concurrent FR 25 FR 25 schedule prior to the determination of each dose–response curve and after the determination of each dose–response curve. These test sessions were intended to measure the effect of the schedule change on the stability of the stimulus control of behavior under baseline training conditions. Drug-substitution tests were conducted in single test sessions on different days for each dose for each pigeon. All dose levels for a single drug were studied before exposure to a different drug. The order of testing was pentobarbital, methamphetamine, chlordiazepoxide, ethanol, PCP, pentobarbital (replication), and PCP (replication). The training and test sessions were terminated after 50 reinforcers had been delivered, or after 40 min, whichever occurred first.

Data Analysis

The number of CODs, the number of responses on each key, the time spent responding under each FR component, and the number of reinforcers earned under each schedule component were recorded. From these data, other measures could be derived. One derived measure was the percentage of responses on the pentobarbital-biased key. The pentobarbital-biased key was defined as the key associated with the FR 10 component after the administration of pentobarbital during the training sessions. The saline-biased key was defined in the same manner as the key associated with the FR 10 component after administration of saline during the training sessions. The percentage of responding on the pentobarbital-biased key was derived from dividing the number of responses emitted on the pentobarbital-biased key by the total number of responses emitted on both keys and converting the proportion to a percentage. A second measure was the percentage of time allocated to responding on the pentobarbital-biased key. A response on the pentobarbital-biased key began the recording of the accumulation of time until a response on the saline-biased key switched the recording of the accumulation of time to the other key. The total time accumulated after responses on the pentobarbital-biased key was divided by the accumulated time spent responding on both keys to calculate the percentage of time spent responding on the pentobarbital-biased key. The total number of responses on a key was divided by the time spent respond-

Table 1

Mean and standard deviation (in parentheses) of the number of reinforcers earned (out of 50) under the FR 40 component of the concurrent FR 10 FR 40 schedules during training sessions after saline or pentobarbital administration for the first 35 sessions of training, the next 20 sessions of stable baseline performance, and the 51 to 180 training sessions conducted while drug substitution tests were being conducted.

		Training sessions		
Pigeon	Treatment	First 35 sessions	Next 20 sessions	During testing
P339	Saline	0.76 (1.09)	0.00 (0.00)	0.32 (1.06)
	Pentobarbital	0.00 (0.00)	0.70 (1.61)	0.48 (2.79)
P340	Saline	3.88 (4.81)	4.80 (3.33)	1.88 (2.47)
	Pentobarbital	0.06 (0.24)	0.00 (0.00)	0.61 (1.56)
P341	Saline	1.71 (5.81)	0.60 (1.58)	0.40 (1.65)
	Pentobarbital	1.00 (3.39)	0.00 (0.00)	0.32 (0.84)
P342	Saline	1.06 (2.79)	0.80 (2.53)	0.15 (0.46)
	Pentobarbital	0.47 (1.07)	0.00 (0.00)	0.29 (1.23)

ing on that key to calculate the rate of responding on the pentobarbital-biased key and the saline-biased key. The sum of the number of responses on the two keys was divided by the total time spent responding on the two keys to calculate the overall rate of responding.

Drugs

Pentobarbital sodium (Sigma Chemical Co.) at doses of 1.0, 3.0, 5.6, 7.8, 10.0, and 13.0 mg/kg (first determination of dose–response effects) or 1.0, 1.8, 3.0, and 5.6 mg/kg (second determination of dose–response effects); PCP hydrochloride (HCl) (National Institute on Drug Abuse) at doses of 0.1, 0.3, 0.56, 0.78, 1.0, and 1.8 mg/kg (both determinations of PCP effects); methamphetamine HCl (Sigma Chemical Co.) at doses of 0.3, 1.0, 1.8, and 3.0 mg/kg; chlordiazepoxide HCl (Hoffman-La Roche, Inc.) at doses of 1.0, 3.0, 5.6, 7.8, and 10.0 mg/kg; and ethanol at doses of 0.25, 0.5, 0.75, and 1.0 g/kg were studied. All drugs except ethanol were dissolved in 0.9% physiological saline to a concentration allowing an injection volume of 1 ml/kg and administered intramuscularly into a breast muscle. Physiological saline was used for vehicle control injections. Doses are expressed as the salt forms of the drugs, except for ethanol. Ethanol (100% wt/vol) was diluted to a 10% wt/vol solution with tap water. The 10% ethanol solution or tap water, which was used as the vehicle control, was administered through a rubber tube that passed down the esophagus into the proventriculus 15 min prior to session initiation. As in training sessions, test session doses were administered 10 min before the session and the pigeons were in the test chamber during the 10-min presession period.

RESULTS

The pigeons learned the pentobarbital discrimination rapidly, and within a few training sessions under the concurrent FR 10 FR 40 schedule confined most of their responses to the key on which responses were reinforced under the FR 10 component. Table 1 shows that during the first 35 training sessions, the birds earned most of the 50 reinforcers available by responding on the FR 10 component of the schedule; however, all birds earned some reinforcers under the FR 40 component. Only Bird P339 averaged less than one reinforcer per session under the FR 40 component after both saline and pentobarbital during this period. All other birds averaged more than one reinforcer per session under the FR 40 component after pentobarbital or saline.

During the final 20 sessions before drug-substitution tests were conducted, all pigeons earned less than one reinforcer per session for responding under the FR 40 component with one exception. Bird P340 earned an average of 4.8 reinforcers per session for responding under the FR 40 component after saline administration. The final column of Table 1 shows that even during the 11 months during which drug-substitution tests were

Table 2

Mean percentages of responses, reinforcers earned, and time (in seconds) spent responding on the pentobarbital-biased key; mean response rates under each component of the concurrent FR 10 FR 40 schedule; and the mean number of changeover delays (CODs) per session for each pigeon in the last 10 training sessions with pentobarbital and 10 training sessions with saline before the beginning of test sessions.

Training condition	Pigeon	Pentobarbital-biased percentage			Responses per second		CODs
		Responses	Reinforcers	Time	FR 10	FR 40	
Pentobarbital	P339	95	99	96	3.21	3.62	1
	P340	100	100	100	2.11	0.00	0
	P341	99	100	99	2.45	5.00	2
	P342	98	100	98	2.29	0.75	1
Saline	P339	1	0	2	2.60	1.20	3
	P340	29	10	36	2.39	1.49	10
	P341	5	1	6	2.02	1.26	2
	P342	6	2	7	2.42	2.15	6

conducted, all birds occasionally continued to receive reinforcers for responding under the FR 40 component. Across birds and training conditions, about 0.5 reinforcers per session were delivered under the FR 40 component, which is about one reinforcer every two training sessions. Thus, throughout these experiments, although most reinforcers were earned for responding on the key on which responses were reinforced under the FR 10 component of the schedule, some reinforcers were earned during training sessions for responding under the FR 40 component of the schedule for all birds during all phases of the experiments.

Table 2 shows more detailed data from the 20 training sessions (10 after saline and 10 after pentobarbital) that occurred immediately preceding the determination of dose–effect curves in the drug-substitution tests. After pentobarbital administration, pigeons averaged 95% to 100% of their responses on the pentobarbital-biased key, averaged 99% to 100% of their reinforcers following responses on the pentobarbital-biased key, and allotted 96% to 100% of their time to responding on the pentobarbital-biased key. These birds rarely switched keys after pentobarbital administration, so mean CODs ranged from zero to two per session. Rates of responding under the FR 10 schedule after pentobarbital administration averaged from 2.11 to 3.21 responses per second. Rates of responding under the FR 40 component were highly variable, ranging from 0.75 to 5.00 responses per second in birds that responded under this component. Although 3 of the 4 birds made some responses under the FR 40 component, only Bird P339 responded enough to produce the reinforcer under this component during the 10 sessions after pentobarbital administration.

After saline administration the pigeons averaged 71% to 99% of their responses on the saline-biased key, averaged 90% to 100% of their reinforcers by responding on this key, and allotted 64% to 98% of their time responding on this key. Although the number of CODs remained low, it was higher for most birds for the saline training sessions than for the pentobarbital training sessions, which is consistent with the birds earning some reinforcers under the FR 40 component of the schedule. Rates of responding under the FR 10 component of the schedule during these training sessions were similar to those during the pentobarbital training sessions. Rates of responding under the FR 10 component averaged between 2.02 and 2.60 responses per second. Thus, the pigeons responded largely on the key on which responses were reinforced under the FR 10 component of the concurrent schedule during training sessions after the administration of both pentobarbital and saline; however, some responding did occur on the other key, and occasionally responses were reinforced under the FR 40 component.

Figure 1 shows the effects of increasing doses of pentobarbital on the percentage of responses on the pentobarbital-biased key. Changing the schedule from concurrent FR

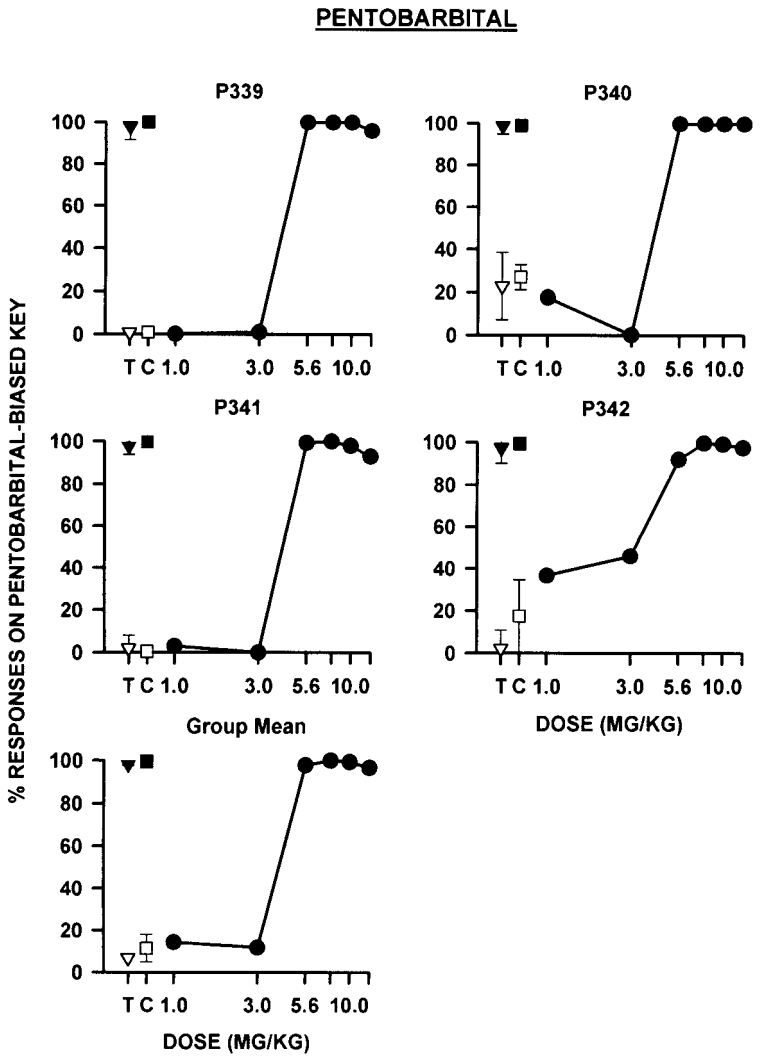

Fig. 1. The dose–response curve for the effects of pentobarbital on the percentage of responses on the key on which responses were reinforced under the FR 10 component of the concurrent FR 10 FR 40 schedule after pentobarbital administration during training for Birds P339, P340, P341, P342, and the group mean. Abscissa: dose (mg/kg) of pentobarbital, log scale. Ordinates: percentage of responses on pentobarbital-biased key. Brackets at T show ± standard deviation around the mean based on the data obtained during training sessions. Brackets at C show ± standard deviation around the mean based on the control sessions in which the schedule was changed to concurrent FR 25 FR 25, which was the schedule used during determination of the dose–response curves. The filled circles show the pentobarbital dose–response curve. The filled triangles and squares above T and C show the effects of 5.0 mg/kg pentobarbital used during training and control sessions. The open triangles and squares above T and C show the effects of saline injections during training and control sessions.

10 FR 40 to concurrent FR 25 FR 25 had little effect on stimulus control exerted by the presence or absence of the training dose of pentobarbital, as shown by comparing the means for training sessions with the data in the control test sessions under concurrent FR 25 FR 25 (Figure 1).

When the pentobarbital generalization curve was determined for Birds P339, P340, and P341, responses were largely confined to the saline-biased key at doses of 1.0 and 3.0 mg/kg. At 5.6 mg/kg pentobarbital, all birds switched almost completely from responding on the saline-biased key to responding on the pentobarbital-biased key. Bird P342 responded slightly more frequently on the pentobar-

bital-biased key after the 1.0 and 3.0 mg/kg doses occurred during saline training sessions, although most responses still occurred on the saline-biased key. However, this bird also switched almost completely to responding on the pentobarbital-biased key after 5.6 mg/kg and higher doses of pentobarbital. Thus, after the low doses of pentobarbital all birds responded on the pentobarbital-biased key at the same low rates seen during training sessions after saline administration. At higher doses of pentobarbital all birds responded on the pentobarbital-biased key at the same high percentages seen during training sessions after administration of the pentobarbital training dose. This switch from responding on the saline-biased key to responding on the pentobarbital-biased key as the dose of pentobarbital increased occurred without the appearance of points on the dose–response curve that were intermediate between performances during saline and pentobarbital control sessions. This switch from responding on the saline-biased key to responding on the pentobarbital-biased key resulted in a steep dose–response curve without intermediate points.

The dose–response curves for time allotted to responding on the pentobarbital-biased key are almost identical to the curves for the percentage of responses on the pentobarbital-biased key after pentobarbital administration that were shown in Figure 1 (data not shown). These dose–response curves shifted from saline- to pentobarbital-like responding without intermediate points on the dose–response curve, especially for Birds P339, P340, and P341. The dose–response curves for the percentage of reinforcers earned for responding on the pentobarbital-biased key also were almost identical to those for percentage of time spent responding on the pentobarbital-biased key (data not shown).

Table 3 shows the data on CODs and rates of responding (averaged across both keys) for all drugs. For pentobarbital, the 13 mg/kg dose increased CODs for Birds P339 and P341. Doses of 3 mg/kg and higher decreased CODs for P340. With the exception of the 7.8 mg/kg dose of pentobarbital for Bird P342, the frequencies of CODs after all other doses of pentobarbital were similar to those observed after saline administration. Pentobarbital decreased response rates only for Bird P339 after the highest dose. There was a tendency for all birds to show small increases in rates of responding at doses in the middle of the dose–response curve.

Figure 2 shows the effects of chlordiazepoxide on responding on the pentobarbital-biased key. All birds responded on the saline-biased key at rates similar to those seen during saline training sessions after the 1.0 mg/kg dose of chlordiazepoxide. Bird P341 switched to the pentobarbital key after the 3.0 mg/kg dose, and Birds P339 and P340 switched after the 5.6 mg/kg dose. The switch from the saline-biased key to the pentobarbital-biased key typically occurred without intermediate points on the dose–effect curve. All data points for the percentage of time spent responding on the pentobarbital-biased key and the percentage of reinforcers earned for responding on the pentobarbital-biased key were almost perfectly superimposed over the points for the percentage of responses on the pentobarbital-biased key (data not shown).

Table 3 shows the effects of increasing doses of chlordiazepoxide on CODs and overall rates of responding. The number of CODs increased slightly after the 7.8 mg/kg dose of chlordiazepoxide for Bird P340 and after the 5.6 and 10 mg/kg doses for Bird P341. Otherwise, CODs were not much affected by changes in the dose of chlordiazepoxide. Chlordiazepoxide had little effect on overall rates of responding.

Figure 3 shows the effects of increasing doses of ethanol on responding on the pentobarbital-biased key. After the 0.25 g/kg dose, all birds responded almost exclusively on the saline-biased key. Birds P339 and P341 shifted to responding primarily on the pentobarbital-biased key after the 0.5 g/kg dose, and Bird P340 shifted after the 1.0 g/kg dose. Even at the higher doses of ethanol, responding by P341 did not quite reach the same level of responding on the pentobarbital-biased key that occurred during pentobarbital training sessions and control sessions, as had occurred for the other 2 birds. As with pentobarbital and chlordiazepoxide, the ethanol dose–response curve was characterized by a switch from responding on the saline-biased key to responding on the pentobarbital-biased key without intermediate points on the dose–response curve.

Table 3 shows the dose–response data for

Table 3

Effects of drugs on changeover delays (CODs or key switches) and overall response rates for individual pigeons from single test sessions under the concurrent FR 25 FR 25 schedule. The 0.0 mg/kg tests were preceded by administration of the drug's vehicle.

Drug	Dose (mg/kg)	Number of CODs				Responses per second			
		P339	P340	P341	P342	P339	P340	P341	P342
Pentobarbital	0.0	5	17	2	16	2.22	1.69	1.83	1.87
	1.0	2	15	3	20	2.67	1.78	1.84	1.87
	3.0	6	1	0	11	2.48	1.78	2.02	1.89
	5.6	0	0	7	11	3.82	2.02	2.47	1.61
	7.8	0	1	0	4	2.54	1.86	2.43	2.28
	10.0	0	0	2	13	2.53	1.89	2.54	1.97
	13.0	44	0	33	11	0.59	2.09	1.98	1.90
Chlordiazepoxide	0.0	10	12	4	—[a]	1.97	1.81	1.92	—
	1.0	4	5	7	—	2.22	1.88	2.00	—
	3.0	3	5	5	—	1.96	1.84	2.03	—
	5.6	9	12	13	—	2.17	1.90	1.75	—
	7.8	2	20	3	—	2.25	1.81	1.97	—
	10.0	9	9	10	—	1.80	2.15	1.50	—
Ethanol[b]	0.0	3	6	0	—	2.35	1.82	1.91	—
	0.25	1	0	0	—	2.50	2.33	2.09	—
	0.5	3	2	12	—	2.14	2.19	2.07	—
	0.75	1	0	7	—	2.48	2.13	2.18	—
	1.0	4	3	11	—	2.01	1.60	1.81	—
Phencyclidine	0.0	8	10	2	—	2.28	2.07	2.06	—
	0.1	16	5	0	—	2.43	1.71	1.71	—
	0.3	39	6	0	—	2.85	2.41	1.81	—
	0.56	32	0	0	—	1.57	2.07	1.91	—
	0.78	2	9	4	—	1.89	1.92	2.49	—
	1.0	13	11	—	—	1.39	1.83	—	—
	1.8	17	45	—	—	0.38	0.61	—	—
Phencyclidine (replication)	0.0	—	14	4	—	—	1.87	2.10	—
	0.1	—	6	5	—	—	2.41	2.57	—
	0.3	—	4	0	—	—	2.04	3.00	—
	0.56	—	4	2	—	—	2.06	2.14	—
	0.78	—	21	5	—	—	1.92	2.30	—
	1.0	—	10	—	—	—	1.90	—	—
	1.8	—	26	—	—	—	1.30	—	—
Methamphetamine	0.0	7	9	0	5	2.15	1.77	2.02	1.82
	0.3	8	6	0	0	2.32	1.91	2.12	1.78
	1.0	15	2	0	0	2.18	1.92	2.13	1.69
	1.8	0	7	1	—	2.04	1.66	2.16	—
	3.0	10	9	0	0[c]	1.88	1.71	1.70	1.39
Pentobarbital (replication)	0.0	6	11	7	—	2.55	1.74	2.30	—
	1.0	14	4	0	—	2.20	1.98	2.22	—
	1.8	2	7	5	—	2.31	1.98	1.83	—
	3.0	3	1	3	—	2.51	1.92	2.41	—
	5.6	0	0	0	—	2.75	2.08	3.60	—

[a] Signifies not tested.
[b] kg dose.
[c] Bird 342 died after the testing of this dose.

the effects of ethanol on CODs and overall response rates. Bird P341 showed small increases in the frequency of CODs after 0.5 and 1.0 g/kg doses. The frequency of CODs was slightly decreased by some doses of ethanol in the other 2 birds. Ethanol had little effect on overall rates of responding.

Figure 4 shows the effects of PCP on responding on the pentobarbital-biased key. All birds responded largely on the saline-biased key after doses from 0.1 mg/kg to 0.78 mg/kg (filled points, first determination). Birds P339 and P340 made slightly more than 50% of their responses on the pentobarbital-bi-

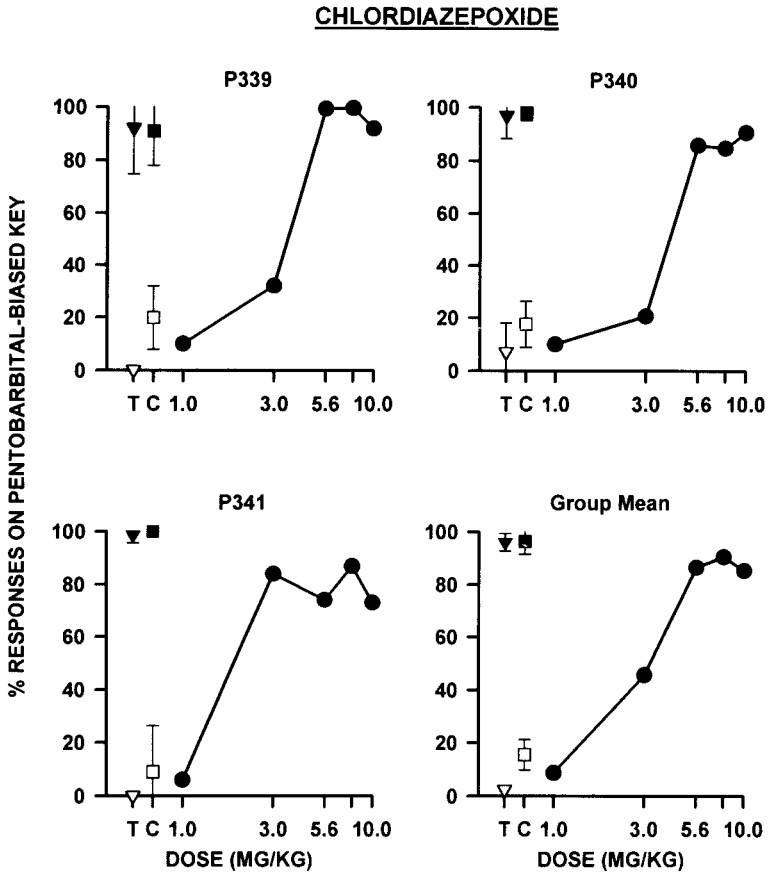

Fig. 2. The dose–response curve for the effects of chlordiazepoxide on the percentage of responses on the key on which responses were reinforced under the FR 10 component of the concurrent FR 10 FR 40 schedule after pentobarbital administration during training sessions. Abscissa: dose (mg/kg) of chlordiazepoxide, log scale. Ordinates: percentage of responding on pentobarbital-biased key. Other details are as in Figure 1.

ased key after the 1.0 and 1.8 mg/kg doses of PCP, although the dose–response curve for Bird P340 turned over at the highest dose. Bird P341 responded almost exclusively on the saline-biased key at all doses of PCP when responding occurred. Because of the individual differences and irregularity of these dose–effect curves, the PCP curves for Birds P340 and P341 were redetermined. This time Bird P341 showed partial generalization to the pentobarbital training stimulus and P340 did not.

Table 3 shows the effects of PCP on the number of CODs and the overall rate of responding on the two keys. PCP produced small increases in the number of CODs, especially during the first determination of the dose–response curve for Birds P339 and P340. Doses of 1.0 and 1.8 mg/kg decreased the rate of responding by Bird P339, and the 1.8 mg/kg dose also decreased the rate of responding by Bird P340.

Figure 5 shows the effects of increasing doses of methamphetamine on responding on the pentobarbital-biased key. None of the pigeons responded more frequently on the pentobarbital-biased key than occurred during saline control sessions at any dose of methamphetamine.

Table 3 shows the effects of methamphetamine on the number of CODs and the overall rate of responding. Methamphetamine did not produce consistent effects on the number of CODs. The highest dose of methamphetamine studied (3.0 mg/kg) produced small decreases in rates of responding by most birds.

After completion of the experiments in

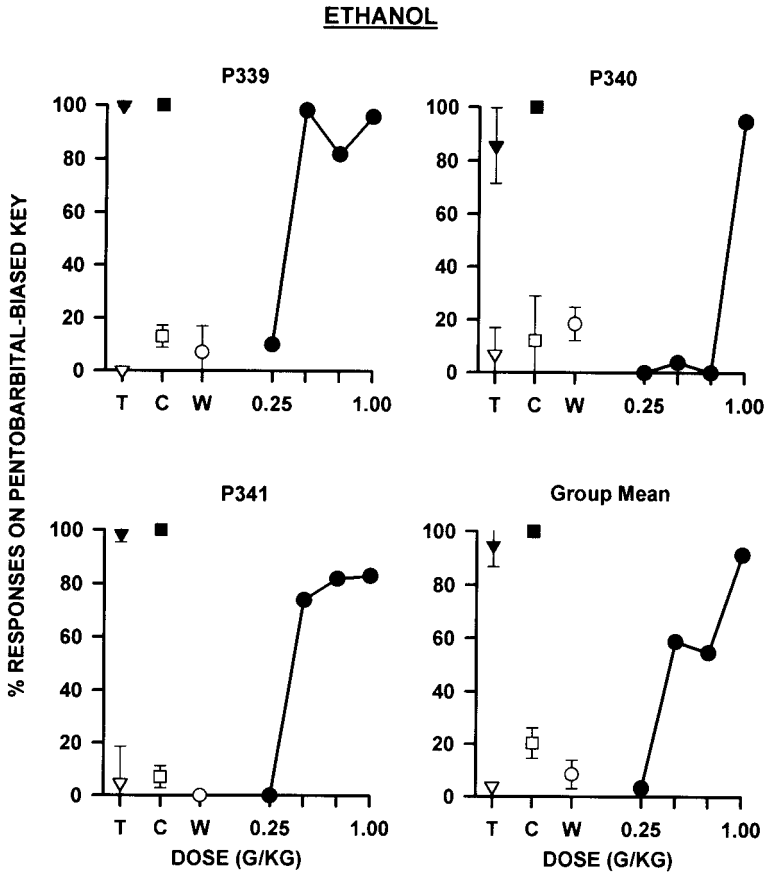

Fig. 3. The dose–response curve for the effects of ethanol on the percentage of responses on the key on which responses were reinforced under the FR 10 component of the concurrent FR 10 FR 40 after pentobarbital administration during training sessions. Abscissa: dose (g/kg) of ethanol, log scale. Ordinates: percentage of responding on pentobarbital-biased key. Brackets at W represent ± standard deviation around the tap water control mean (open circles), which is based on four observations after tap water was administered down the esophagus into the proventriculus. Other details are as in Figure 1.

which other drugs were substituted for the training dose of pentobarbital were completed, the pentobarbital dose–response curve was redetermined. The effects of pentobarbital on responding on the pentobarbital-biased key (Figure 6) were very similar to its effects the first time that this dose–response curve was determined (Figure 1). All birds shifted from responding predominantly on the saline-biased key after low doses of pentobarbital to responding predominantly on the pentobarbital-biased key after higher doses of pentobarbital. The switch from responding on the saline-biased key to responding on the pentobarbital-biased key occurred at 3.0 mg/kg pentobarbital for Birds P339 and P340 and at 5.6 mg/kg pentobarbital for P341 without intermediate points on the dose–response curve. The effects of pentobarbital on CODs was also very similar to the effects obtained during the initial dose–response determination (Table 3).

There was a difference in control performance associated with the initial pentobarbital dose–response curve and the redetermination of this curve. During training sessions under concurrent FR 10 FR 40 and control sessions under concurrent FR 25 FR 25 associated with the first determination of the pentobarbital dose–response curve, the percentage of responses on the pentobarbital-biased key was very similar under the concurrent FR 10 FR 40 schedule and the concurrent FR 25 FR 25 schedule. When the

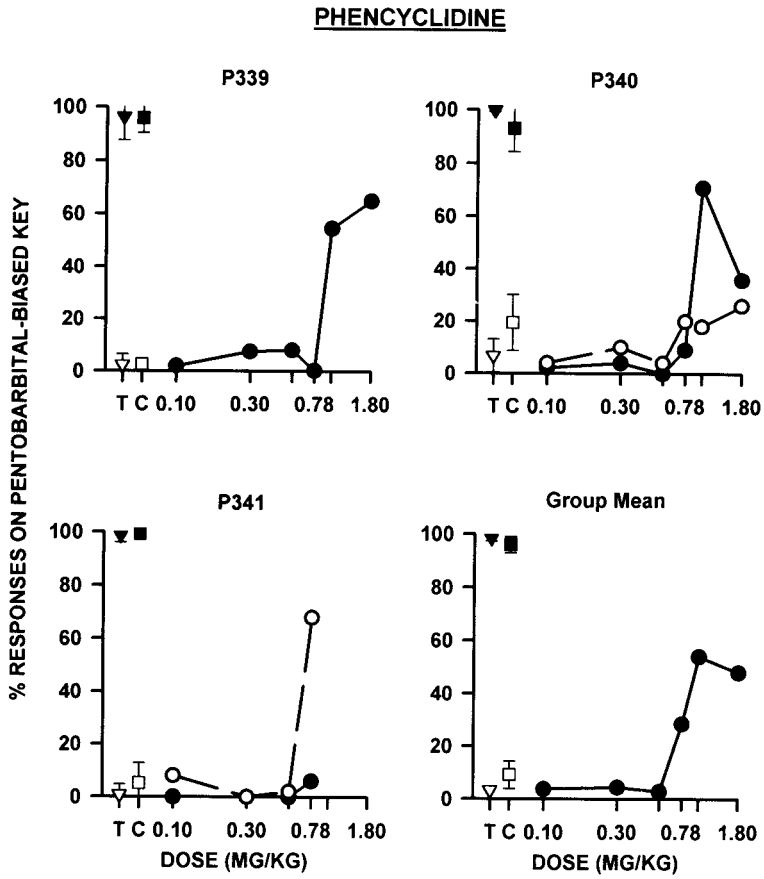

Fig. 4. The dose–response curve for the effects of PCP on the percentage of responses on the key on which responses were reinforced under the FR 10 component of the concurrent FR 10 FR 40 schedule after pentobarbital administration during training sessions. The filled circles show the first determination of the PCP dose–response curve, and the open circles show the redetermination of the dose–response curve. Abscissa: dose (mg/kg) of PCP, log scale. Ordinates: percentage of responding on pentobarbital-biased key. Other details are as in Figure 1.

pentobarbital dose–response curve was redetermined, more responding occurred on the pentobarbital-biased key after saline administration under the concurrent FR 25 FR 25 schedule than under the FR 10 FR 40 schedule. This difference in control performance under the concurrent FR 10 FR 40 and the concurrent FR 25 FR 25 schedules was not observed after pentobarbital administration.

DISCUSSION

Pigeons rapidly learned to discriminate 5.0 mg/kg pentobarbital from saline under a concurrent FR 10 FR 40 schedule of food presentation, as shown by the high proportion of responses made on the response key associated with the FR 10 component of the concurrent schedule after administration of both saline and training doses of pentobarbital. Although the discrimination was learned rapidly, during training the birds sometimes did complete 40 or more responses on the key on which the FR 40 schedule was in effect and received reinforcers for responding on this key. Reinforcers also were delivered occasionally for responding on the FR 40 component of the schedule even after extended training. Thus, all pigeons received reinforcers following responses on both components of the concurrent schedule during early training sessions and when responding had stabilized, although the percentage of reinforcers delivered during training sessions for responding under the FR 10 component of

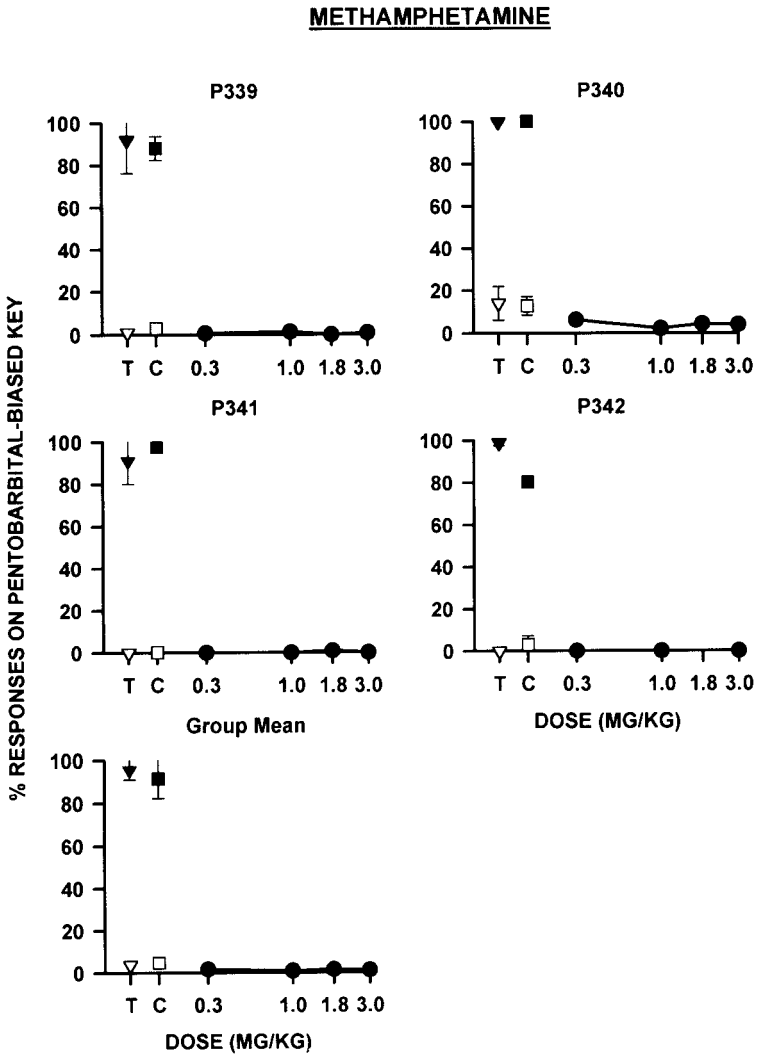

Fig. 5. The dose–response curve for the effects of methamphetamine on the percentage of responses on the key on which responses were reinforced under the FR 10 component of the concurrent FR 10 FR 40 schedule after pentobarbital administration during training sessions. Abscissa: dose (mg/kg) of methamphetamine, log scale. Ordinates: percentage of responding on pentobarbital-biased key. Other details are as in Figure 1.

the concurrent schedule was much higher than that under the FR 40 component.

Changing the schedule of reinforcement during test sessions did not disrupt stimulus control by the presence or absence of the training drug, although there is some indication that with repeated exposure to the concurrent FR 25 FR 25 schedule following the administration of saline there was a slight increase in the percentage of responses on the pentobarbital-biased key. For example, when saline was given in association with the first determination of the pentobarbital dose–response curve, the percentage of responses on the pentobarbital-biased key was very similar under concurrent FR 10 FR 40 and concurrent FR 25 FR 25. In later drug tests, more responding occurred on the pentobarbital-biased key after saline administration when the schedule was concurrent FR 25 FR 25 than when the schedule was concurrent FR 10 FR 40 (Figure 6). These data suggest that with repeated exposure to testing under concurrent FR 25 FR 25, the schedule change was beginning to change the pattern of responding on the two keys during test ses-

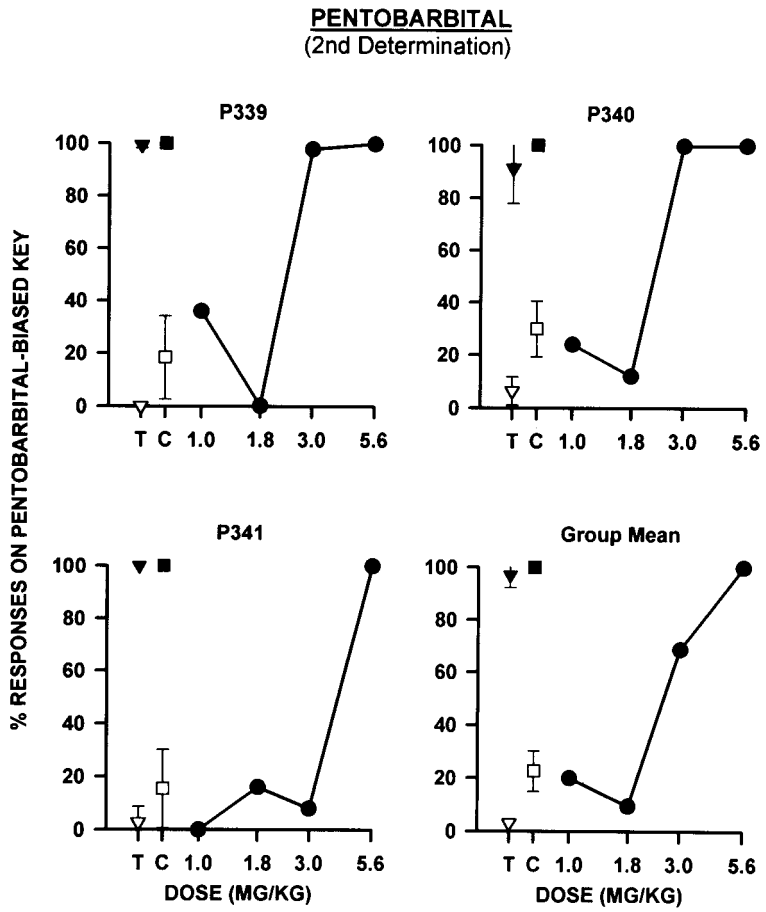

Fig. 6. The dose–response curve for the redetermination of the effects of pentobarbital on the percentage of responses on the key on which responses were reinforced on the FR 10 component of the concurrent FR 10 FR 40 schedule after pentobarbital administration during training sessions. Abscissa: dose (mg/kg) of pentobarbital, log scale. Ordinates: percentage of responding on the pentobarbital-biased key. Other details are as in Figure 1.

sions. If this effect became more pronounced with repeated test sessions under concurrent FR 25 FR 25, it might explain why more responding occurred on the pentobarbital-biased key after low doses of pentobarbital the second time that the dose–response curve was determined than the first time the dose–response curve was determined. Why this effect occurred after saline and low doses of pentobarbital, but not after the training dose and higher doses of pentobarbital, is not known. Nevertheless, the presence or absence of pentobarbital exerted strong stimulus control throughout the experiment, despite this small increase in responding on the pentobarbital-biased key when saline or low doses of pentobarbital were administered before test sessions.

In the present experiments, the pentobarbital dose–response curves were quantal in shape. Low doses of pentobarbital produced responding that was not different from that during saline training sessions. As the dose of pentobarbital increased, there was little change until a dose was reached at which responding occurred at near maximal levels on the pentobarbital-biased key. This produced an all-or-nothing dose–response curve rather than a graded dose–effect curve.

This research has a number of implications. First, pigeons can be trained to discriminate pentobarbital from saline under the relative reinforcement contingencies of concurrent FR FR schedules. This adds to the generality of previous findings that pigeons can learn drug discriminations under the relative rein-

forcement contingencies provided by concurrent VI VI schedules (Snodgrass & McMillan, 1996) and concurrent FI FI schedules (McMillan et al., 1997).

Second, these data show that quantal responding can occur under conditions of relative reinforcement. Colpaert (1991) and Mathis and Emmett-Oglesby (1990) have suggested that quantal responding occurs in drug-discrimination studies because responses on the drug key are reinforced only in the presence of the training drug and responses on the saline key are reinforced only in the absence of the training drug. These FR and extinction contingencies could be the basis for the quantal dose–response curves observed in many drug-discrimination experiments. In the present experiments, responses on the key with the higher FR value were reinforced occasionally during training sessions conducted after both pentobarbital and saline administration, yet quantal dose–response curves were obtained. Thus the present experiments suggest that the extinction of responses that occur on the ''incorrect'' key during training is not a necessary condition for quantal responding to develop. Conversely, the extinction of responses on the incorrect key does not assure that quantal responding will develop, as shown by the graded pattern of responding that develops under concurrent FI extinction schedules (Massey et al., 1992).

We now have collected a considerable amount of data that suggests that the schedule of reinforcement is an important determinant of the shape of the dose–effect curve in drug-discrimination studies. When animals have been trained using interval schedules on the key on which responses are reinforced, interval schedules generate graded dose–effect curves. We have shown this to be true using FI schedules in pigeons and rats (Massey et al., 1992; Snodgrass & McMillan, 1991). These effects have been confirmed with simple FI schedules (Massey et al., 1992), with the FI component of a multiple schedule (McMillan & Hardwick, 1996; Snodgrass & McMillan, 1991), and with concurrent interval schedules (McMillan et al., 1997; Snodgrass & McMillan, 1996). The effects appear to be independent of FI size (McMillan & Hardwick, 1996). They occur under both FI and VI schedules (Massey et al., 1992; Snodgrass & McMillan, 1991, 1996).

Conversely, when animals have been trained using FR schedules on the key on which responses are reinforced, quantal dose–response curves are generated. These effects have been observed in pigeons and rats with both simple FR schedules and the FR component of a multiple schedule (Massey et al., 1992; Snodgrass & McMillan, 1991; and a host of experiments in the literature using simple FR schedules) and across a range of ratio sizes, although there is some tendency for ratios with very high response requirements to generate responding that is more ''interval like'' (McMillan & Hardwick, 1996). The effects have been observed under simple FR schedules (Massey et al., 1992), the FR component of a multiple schedule (McMillan & Hardwick, 1996; Snodgrass & McMillan, 1991), second-order FR schedules (McMillan, Cole-Fullenwider, Hardwick, & Wenger, 1982), and now with concurrent FR schedules. The importance of this finding is that it is the schedule of reinforcement that appears to control the shape of the drug-discrimination dose–response curve, rather than some inherent property of drug stimuli. Clearly, drug stimuli can be varied quantitatively, and animals are sensitive to these variations in stimulus intensity as shown by their ability to discriminate between different doses of the same drug (Colpaert & Janssen, 1982; Young, Walton, & Perkins, 1989). However, whether the animal's behavior in the usual two-choice drug-discrimination procedure is controlled by these variations in the intensity of the drug stimulus to produce graded responding, or is controlled by the presence or absence of the drug stimulus above some threshold intensity to produce quantal responding, depends largely on the schedule of reinforcement. Under ratio schedules, quantal responding is likely to occur with the switch from responding on the saline-biased key to responding on the drug-biased key occurring above a threshold dose. Under interval schedules, graded responding occurs and the degree to which the animal responds on the drug key is a joint function of the stimulus intensity and the reinforcement schedule. This explanation seems to have wide generality in situations in which the subject is trained to discriminate drug

from saline. Whether it also applies when the discrimination is between two drugs, or between two doses of the same drug, remains to be determined.

How can exceptions to this ''rule'' be explained? For example, McMillan et al. (1982) used second-order FR schedules to study PCP discrimination in pigeons. As would be expected from the previous discussion, most dose–response curves were quantal; however, one of the eight curves was graded rather than quantal. It is possible that the intensity of the drug stimulus can wax and wane, or that the subject's attention to the drug stimulus can increase and decrease, while the animal is responding under FR schedules. These are only speculations that might explain graded responding under FR schedules, and there is no evidence that such mechanisms actually contribute to the development of graded dose–response curves under FR schedules.

When other drugs were substituted for pentobarbital, they produced effects similar to those reported under simple FR schedules. Chlordiazepoxide and ethanol generalized to pentobarbital as expected, based on reports of the similarity of the discriminative stimulus properties of barbiturates, benzodiazepines, and ethanol (De Vry & Slangen, 1986; Grech & Balster, 1993; Jarbe & McMillan, 1983; Overton, 1966). As predicted, the shape of the dose–effect curves for ethanol and chlordiazepoxide was quantal in the present studies. Methamphetamine did not generalize to pentobarbital, which is similar to the findings of others with amphetamines and barbiturates (Witkin, Carter, & Dykstra, 1980). PCP showed partial generalization to pentobarbital in that at some doses of PCP more than 50% of the responding occurred on the pentobarbital-biased key, which is similar to our previous observations (McMillan, 1982; Snodgrass & McMillan, 1991). These data suggest that the concurrent FR FR schedule generates PCP discrimination data that are similar to PCP data obtained under other FR schedules. However, other than extending our hypothesis that FR schedules generate quantal dose–response curves in drug-discrimination experiments, the concurrent FR FR schedule appears to offer few advantages over simple schedules that would recommend its routine use in drug-discrimination research.

The partial generalization of the pentobarbital stimulus to PCP is intriguing. After low doses of PCP, responding was largely confined to the saline-biased key, but after higher doses, responding occurred on both keys, although the effects were not consistent across replications in the same bird. Thus, responding on the pentobarbital-biased key never reached the levels seen after the administration of the training dose of pentobarbital. One explanation for this finding could be that PCP produces a stimulus that is only somewhat like that of pentobarbital, and the ''intermediate responding'' is a reflection of this partial similarity. A related possibility is that this intermediate responding represents the asymptote of a quantal dose–response curve for PCP that does not reach the same maximum seen with pentobarbital, because PCP cannot substitute completely for pentobarbital. According to this view, mixed responding on the two keys would represent the limited efficacy of PCP as a pentobarbital-like stimulus. Colpaert (1991) has suggested that mixed responding on the drug key and saline key after PCP administration in rats trained to discriminate fentanyl from saline results from a loss of stimulus control over responding, which is another possible explanation of the current results. Our data do not permit us to select among these and other alternative explanations for the partial generalization observed after PCP administration.

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